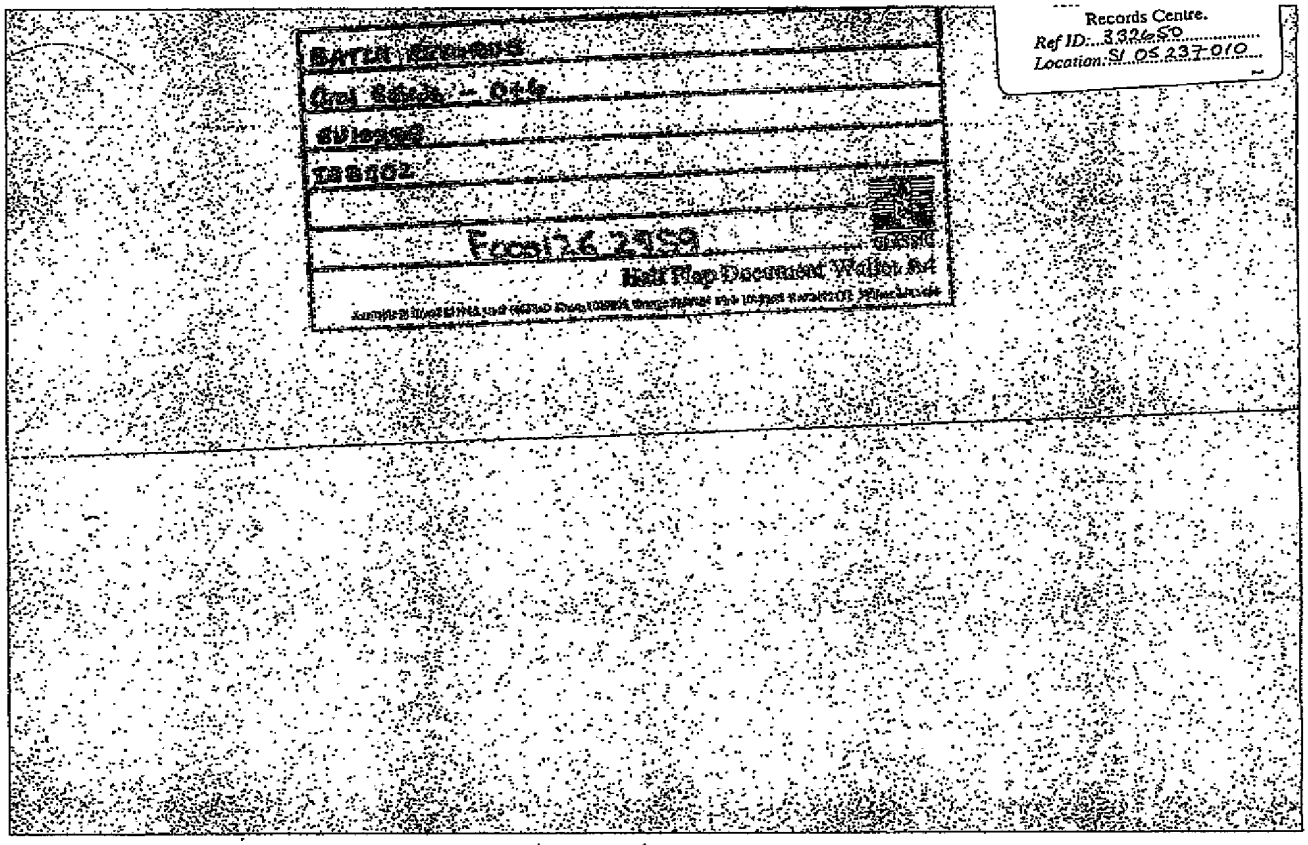
ANNEX 2

F0001262959 - I83G02



Pharmacia & Upjohn

Pharmaceutical Development / *Oral solids and warehousing*

PROCESSING SHEET

PAGE: 1 of *21*

PRODUCT: SU10398 LOT: I83G02

PHARMACEUTICAL FORM: Capsule DOSAGE: 50 mg (as free base) COMM.: *RD0511POSUG*

FORMULA No.: 83HC01 *01/06/2001* [signature] [initials] *12/04/2001* PREPARATION DATE: [initials] *06 April 2001* *04 / 2001* *10/05/2001* *27 / 04 / 01* [initials] *11/05/01*

PROCESSING START: *01 / 04 / 2001*

**CALCULATE BASED ON THE WEIGHT OF AVAILABLE GRANULATE* [initials] 06/06/01

THEORETICAL QUANTITY: *48054* (T) QUANTITY OBTAINED: *61.875* yield: ~~*87.66*~~ *10/05/01 87.14%* %

SCOPE OF THE PREPARATION: Stability studies and clinical trial [signature]

THEORETICAL UNITARY FORMULA

RAW MATERIAL		SPECIFICATIONS	M.U.	UNIT DOSE	Over Dose
GRANULATE AT 75% W/W OF SU10398	Active principle	*LOT I83K01*	*mg*	*89.066*	
CPS: T/C OPAQUE SWEDISH ORANGE GEL Fto 3	Excipient compensation	[initials] 06/04/01	*mg*	*49±4*	
		[initials] *06/04/01*			

Signature of who filled out the form:

[signature]

Edition No.: 7 of 10/05/99
Substitutes Edition No.: 6 of 03/11/97

Approval for use by the Chief of ORAL SOLIDS and WAREHOUSING:

[signature]

Product: SU10398 Lot: I83G02 Page: 2 of 21

Pharmaceutical form: Capsule Dosage: 50 mg (as free base)

PRACTICAL FORMULATION

RAW MATERIALS	CODE	LOT No.	TITER	Over dose	M.U.	PRACTICAL UNIT DOSE*	M.U.	Practical quantity per .....
GRANULATE AT 75% P/ OF SU10398		*I83K01*			*mg*	*89,066*		
T/C OPAQUE SWEDISH ORANGE GEL F. 3	*1491*	*AE283*						
		[initials]	*06/04/01*					

NOTE: **DOSE FOR 1 CPS TAKEN CONSIDERING 75-85 AS THE THEORETICAL RATIO % FREE BASE / SALT.*

Operator's signature: [signature]

Verifier's signature: [signature]

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Checked by: [signature]

Product: SU10398 Lot: I83G02 Page: 3 of 21

Pharmaceutical form: Capsule Dosage: 50 mg (as free base)

CLEANING OF THE EQUIPMENT AND ROOMS

Once the processing has been completed, clean the processing rooms with: *5% PYRONEG AQUEOUS SOLUTION (METHOD 50/CM/019)*

Once the processing has been completed, clean the equipment with: *5% PYRONEG AQUEOUS SOLUTION (METHOD 50/CM/019)*

PROCESSING IDENTIFICATION LABELS

CONFORMITY VERIFICATION LABELS		DATE: *06 / 04 / 01*	SIGNATURE: [signature]	
LABELS DELIVERED	No.: *40*	DATE: *12 / 05 / 01*	SIGNATURE: [signature]	
ADDITIONAL DELIVERED	No.:	DATE: / /	SIGNATURE:	
LABELS USED	No.: *35*	DATE: *10 / 05 / 01*	SIGNATURE: [signature]	
DETERIORATED LABELS	No.:	DATE: / /	SIGNATURE:	
LABELS RETURNED	No.: *5*	DATE: *10 / 05 / 01*	SIGNATURE: [signature]	

(The returned labels are destroyed)

LABEL MODEL

Pharmacia & Upjohn – *Oral Solids Section*

Capsule SU10398 50 mg (as free base)

LOT: I83G02 Prep. Date: 04/2001

FORMULA No.: 83HC01

.....

Date: *12 / 04 / 01* Label No. 8 of 8

[signature]

NOTE:

Pharmacia & Upjohn – *Oral Solids Section*
Product: Granulated SU10398 50 mg (as free base)
LOT: I83K01 Prep. Date: 04/2001
FORMULA No.:
Date: 12 /04 /01 .....
[signature] Label No. 16 of 16

Pharmacia & Upjohn

Pharmaceutical Development / *Oral solids and warehousing*

Product: SU10398 Lot: I83G02 Page: *4* of *21*

Pharmaceutical form: Capsule Dosage: 50 mg (as free base) Room: *72*

WEIGHT VERIFICATION OF THE RAW MATERIALS

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
	1	**Check the weight of the active principle/s**			
	1/1	PRODUCT:	Lot:		
		.....	Gross: .....g		
		LOT:	Tare: ..... g		
		PRACTICAL WEIGHT: ..... g	Net: ..... g		
			Scale ID No.:		
		PRODUCT:	Lot:		
		.....	Gross: .....g		
		LOT:	Tare: ..... g		
	1/2	PRACTICAL WEIGHT: ..... g	Net: ..... g		
		[initials]	Scale ID No.:		
		PRODUCT: *06/04/2001*	Lot:		
		.....	Gross: .....g		
		LOT:	Tare: ..... g		
		PRACTICAL WEIGHT: ..... g	Net: ..... g		
			Scale ID No.:		
		PRODUCT:	Lot:		
	1/3	.....	Gross: .....g		
		LOT:	Tare: ..... g		
		PRACTICAL WEIGHT: ..... g	Net: ..... g		
			Scale ID No.:		
		PRODUCT:	Lot:		
		.....	Gross: .....g		
		LOT:	Tare: ..... g		
		PRACTICAL WEIGHT: ..... g	Net: ..... g		
			Scale ID No.:		

Pharmacia & Upjohn

Pharmaceutical Development / *Oral solids and warehousing*

Product: SU10398 | Lot: I83G02 | Page: 5 of 21

Pharmaceutical form: Capsule | Room: 72 | Dosage: 50 mg (as free base)

WEIGHT VERIFICATION OF THE RAW MATERIALS

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
01 04 12	2	**Check the weight of the following raw materials:**			
	2/1	PRODUCT: *GRANULATE AT 75% P/P OF SU 10398* LOT: *I83K01* PRACTICAL WEIGHT *4280* g	Lot: *I83K01* Gross: *7080* g Tare: *2800* g Net: *4280* g Scale ID No.: *50-BL-32*		
	2/2	PRODUCT: *T/C OPAQUE SWEDISH ORANGE GEL CPS Fto 3* LOT: *AE283* PRACTICAL WEIGHT ~~N/A~~ *3185* g [initials] *12/4/01*	Lot: *AE283* Gross: *3450* g Tare: *260* g Net: *3190* g Scale ID No.: *50-BL-32*		
	2/3	PRODUCT: LOT: PRACTICAL WEIGHT g	Lot: Gross: g Tare: g Net: g Scale ID No.:		
	2/4	PRODUCT: LOT: PRACTICAL WEIGHT g	[initials] *06/04/2001* Lot: Gross: g Tare: g Net: g Scale ID No.:		
	2/5	PRODUCT: LOT: PRACTICAL WEIGHT g	Lot: Gross: g Tare: g Net: g Scale ID No.:		

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Checked by: [signature]

Product: SU10398 Lot: I83G02 Room: Page: 6 of 21

Pharmaceutical form: Capsule Dosage: 50 mg (as a free base) **DISTRIBUTION into CAPSULES**

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
	3	**Distribution into capsules**			
01 09 12	3/1	Verify the conformity of the hard gelatin shells: Format No.: 3 Body: OPAQUE SWEDISH ORANGE Head: OPAQUE SWEDISH ORANGE Printing: /	Conforms: Yes ☒ No ☐	[initials]	
	3/2	Weigh 100 empty shells to determine the average weight.	Average shell weight: 48.2 mg (α)		
	3/3	Make the ZANASI AZ 5 type capsule sealing machine ready and set it to format No. 3 with No. 2 dosage dispensing.	Capsule sealing machine: ZANASI AZ5 ID number: 30-09-05 Cleaning verification: OK Dispenser No.: 2 Format No.: 3	[initials] [initials]	[initials] [initials]
01 04	3/4	Work Parameters 89.066 [initials] 06/04/01 Theoretical weight: 89.166 mg Distribution weight: Theoretical + α Weight limit: β + (± 7.5 % of the theoretical)	Distribution weight: 137.26 mg (β) Top end weight: 143.93 mg Bottom end weight: 130.60 mg	[initials] [initials]	[initials] [initials]
12	3/5	Hopper level height: IN PROCESS mm	Hopper level: ~30 mm	[illegible]	
	3/6	Dispenser chamber height: IN PROCESS mm	Dispenser chamber: 11.84 mm VALUE TAKEN ABOVE THE DISPENSOR 20/04/01		
	3/7	Piston pressure Yes ☒ No ☐	Pressure index: NOT APPLICABLE		
	3/8	Teflon coated pistons Yes ☒ No ☐	Yes ☒ No ☐		
	3/9	Machine speed: 3500 cps/h	Machine speed: 3500 cps/h Production speed: 3500 cps/h		

Edition No.: 7 of 10/05/99
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Checked by: [signature]

Capsules	Lot	[illegible]
12.06.2001		1021
[illegible]		[illegible]

Capsules

n		Value
065	+	0.0
066	+	0.0
067	+	0.0
068	+	0.0
069	+	0.0
070	+	0.0
071	+	0.04
072	+	0.04
073	+	0.04
074	+	0.05
075	−	0.01
076	+	0.01
077	+	0.046
078	+	0.049
079	+	0.048
080	+	0.050
081	+	0.047
082	+	0.047
083	+	0.050
084	−	0.047
085	+	0.049
086	+	0.048
087	+	0.046
088	+	0.048
089	+	0.047
090	+	0.047
091	+	0.048
092	+	0.049
093	+	0.046
094	+	0.048
095	+	0.051
096	+	0.047
097	+	0.045
098	+	0.046
099	+	0.049
100	+	0.050

n	100
x̄	0.0472 g
r.	0.0017 g
rel	2.70 %
Σx	4.716 g
min	0.045 g
max	0.051 g
Diff	0.065 g

Product: SU10398 Lot: I83G02 Room: *72* Page: *7* of *21*

Pharmaceutical form: Capsule Dosage: 50 mg (as a free base)

DISTRIBUTION into CAPSULES

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
01 04 12	*3/10*	During the distribution, guide the produced capsules into a cyclone separator. *AND THEREFORE IN DEPOWDERING. (RECORD THE CHARACTERISTICS IN THE NOTES)* [initials] *06/04/01*	Model: *DS71* ID number: *50/SC/01* Cleaning verification: *OK* Operative parameters: *~ 40-42%*	[initials]	[initials]
	3/11	*FROM THE DEPOWDERING* As they come ~~out of the cyclone~~, collect the capsules in suitable container/s of: *DOUBLE PE BAG AND KRAFT BARREL*	Container used: *PE BAG AND KRAFT BARREL.*		
01 04 12	*4*	**Sampling and controls**		[initials]	[initials]
	4/1	Monitor the processing so that the process is executed within the set parameters and perform the following controls according to the manner indicated in SOP SF.CF 004 and the indications shown on the corresponding section of the form.			
01 04 12	*5*	**Preparations for the sampling of the finished product for controls**		[initials]	[initials]
	5/1	At the beginning, middle and end of the distribution into capsules, sample (in a manner equally spread throughout) an overall number of capsules equal to *about 600* units which are necessary for controls on the finished product.	☒		
01 04 12	*6*	**DISTRIBUTION START**	*12.04.01* Date: ~~*13:30*~~ Time: *13:30* [initials] *12/04/01*	[initials]	[initials]

Checked by: [signature]

Product: SU10398 Lot: I83G02 Room: *78* Page: *8* of *21*

Pharmaceutical form: Capsule Dosage: 50 mg (as a free base)

DISTRIBUTION into CAPSULES

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
	7	**Controls while in process**			
01 04 12	*7/1*	Capsule appearance at the beginning of distribution (that there are no signs of rupture or crushing on the body and/or tips)	Capsule appearance at the beginning of distribution *CONFORMS*	[initials]	[initials]
	7/2	Uniformity of weight/average weight (SOP SF.CI 051)	☒		
	7/3	Disintegration (SOP SF.CI 015)	☒		
	–	Uniformity of contents [initials] ☐ (sample 30 capsules at the beginning – middle – end of distribution and send the samples to SF/Pharmaceutical Controls) *12/04/01*	Beginning ☐ Middle ☐ End ☐		
	7/4	Capsule appearance at the end of distribution (that there are no signs of rupture or crushing on the body and/or tips)	Capsule appearance at the end of distribution *CONFORMS*	[initials]	[initials]

Product: SU10398 | Lot: I83G02 | Room: 72 | Page: 9 of 21

Pharmaceutical form: Capsule | Dosage: 50 mg (as a free base) | **DISTRIBUTION into CAPSULES**

IN PROCESS WEIGHT CONTROLS (SOP SF.CI 051)

Scale model: *SARTORIUS* ID number: *50/BL/37*

Frequency	Avg. theoretical weight	Top end weight	Bottom end weight	No. controls per insp.	No. of Operations
Start/End of processing/day and every *20 MINUTES*	*137.26*	*143.93*	*130.60*	*20*	*7/2*

DATE	TIME	*SEE NOTE* [initials] *14/05/02* SINGLE WEIGHT VALUES										AVG	S.D.	CV%
12.04.01	*13:30*	*135*	*136*	*133*	*131*	*135*	*134*	*135*	*136*	*135*	*134*	*134.25*	*1.33*	*0.99*
		135	*135*	*134*	*134*	*134*	*135*	*131*	*135*	*134*	*134*			
	13:30	*132*	*135*	*137*	*136*	*134*	*135*	*135*	*134*	*136*	*135*			
		MACHINE STOPPED FOR ADHESION PROBLEMS												
18/04/01	*14:07*											*135.7*	*1.50*	*1.11*
	14:28											*135.5*	*1.80*	*1.33*
	15:07											*136.3*	*1.80*	*1.32*
19/04/01	*8:03*											*136.6*	*1.90*	*1.39*
	8:26											*137.3*	*1.80*	*1.31*
	8:54											*137.8*	*2.20*	*1.60*
	9:11	*SEE ATTACHED PRINTOUTS*										*136.5*	*2.10*	*1.54*
	9:56											*136.8*	*1.60*	*1.17*
	10:20											*136.5*	*2.70*	*1.98*
	10:44											*134.2*	*1.90*	*1.42*
	12:49											*136.8*	*2.00*	*1.46*
	13:13	*136*	*138*	*137*	*133*	*134*	*139*	*134*	*135*	*134*	*140*	*136.7*	*2.41*	*1.76*
		139	*138*	*138*	*139*	*133*	*140*	*138*	*139*	*136*	*134*			
	13:30											*138.0*	*2.40*	*1.74*
	13:55											*136.0*	*1.80*	*1.32*
	14:12											*135.7*	*2.70*	*1.99*
	14:32											*134.6*	*1.80*	*1.34*
	15:10											*133.1*	*1.90*	*1.43*
	15:49											*138.1*	*5.30*	*3.84%*
20/04/01	*7:47*											*137.6*	*2.30*	*1.67*
	8:47	*SEE ATTACHED PRINTOUTS*										*140.0*	*1.80*	*1.29*
	8:56											*138.6*	*1.50*	*1.08*
	9:58											*140.0*	*1.50*	*1.07*

OPERATOR'S SIGNATURE: [signature]

VERIFIER'S SIGNATURE: [signature]

Checked by: [signature]

Pharmacia & Upjohn

Pharmaceutical Development / *Oral Solids and Warehousing*

Product: SU10398 | Lot: I83G02 | Room: *72* | Page: *1* of *9*

Pharmaceutical form: Capsule | Dosage: 50 mg (as a free base) | **DISTRIBUTION into CAPSULES**

IN PROCESS WEIGHT CONTROLS (SOP SF.CI 051)

Scale model: *SARTORIUS* ID number: *50/BL/37*

Frequency	Avg. theoretical weight	Top end weight	Bottom end weight	No. controls per insp.	No. of Operations
Start/End of processing/day and every *20 MINUTES*	*137.26*	*143.93*	*130.60*	*20*	*7/2*

DATE	TIME	SINGLE WEIGHT VALUES										AVG	S.D.	CV%
23/04/01	*7:31*											*138.1*	*1.20*	*0.87*
	7:45											*137.1*	*1.60*	*1.17*
	8:01											*137.1*	*1.20*	*0.88*
	8:21											*136.5*	*1.40*	*1.34*
	8:44											*136.8*	*1.80*	*1.32*
	9:07											*136.9*	*2.00*	*1.46*
	9:37											*136.0*	*1.30*	*0.96*
	9:50											*138.8*	*1.70*	*1.22*
	10:18											*137.1*	*1.70*	*1.24*
	10:35											*138.1*	*2.20*	*1.54*
	10:52											*139.0*	*1.70*	*1.22*
	12:34											*139.2*	*1.40*	*1.01*
24/04/01	*8:40*											*139.6*	*1.60*	*1.15*
	8:59	*SEE ATTACHED PRINTOUTS*										*137.6*	*1.50*	*1.09*
	9:30											*135.2*	*1.80*	*1.33*
	10:03											~~*147.3*~~	~~*254.4*~~	~~*139.8*~~
		CORRECT DATA IN 15 VALUES										[initials] ~~*14/05/01*~~		
		135	*135*	*136*	*134*	*136*	*138*	*136*	*135*	*137*	*135*	*135.9*	*1.45*	*1.07*
		138	*136*	*135*	*139*	*134*	*137*	*134*	*137*	*135*				

OPERATOR'S SIGNATURE: [signature]

VERIFIER'S SIGNATURE: [signature]

Edition No.: 7 of 10/05/99
Substitutes edition No.: 6 of 03/11/97

Checked by: [signature]

Product: SU10398	Lot: I83G02	Room: *69*	Page: *10* of *21*
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)		**DISTRIBUTION into CAPSULES**

IN PROCESS DISINTEGRATION CONTROLS (SOP SF.CI 015)

EQUIPMENT: *SOTAX DT3 DISINTEGRATOR* ID number: *50/DS/01*

FREQUENCY	LIMITS	IMMERSION FLUID	No. controls per inspection	No. OPERATIONS
Start/End of processing/day and every *1*	≤ *30* min	*TDI WATER 37 °C*	*6*	*7/3*

DATE	TIME	CONTROLS ON IMMERSION FLUID	SINGLE VALUES					
12-4-01	*13:30*	Temp: *37.2* °C Level: *CONFORMS*	*6'00"*	*6'45"*	*7'00"*	*7'30"*	*8'10"*	*8'30"*
12-4-01	*17:00*	Temp: *37.2* °C Level: *CONFORMS*	*6'00"*	*6'30"*	*7'05"*	*7'20"*	*8'00"*	*8'15"*
18-4-01	*14:00*	Temp: *37.2* °C Level: *CONFORMS*	*6'10"*	*6'35"*	*6'55"*	*7'25"*	*7'55"*	*8'20"*
18-4-01	*17:00*	Temp: *37.2* °C Level: *CONFORMS*	*6'05"*	*6'25"*	*6'50"*	*7'20"*	*7'50"*	*8'15"*
19-4-01	*8:30*	Temp: *37.2* °C Level: *CONFORMS*	*6'00"*	*6'40"*	*6'55"*	*7'15"*	*7'40"*	*8'00"*
19-4-01	*17:00*	Temp: *37.2* °C Level: *CONFORMS*	*6'05"*	*6'30"*	*6'55"*	*7'20"*	*7'45"*	*8'15"*
20-4-01	*8:30*	Temp: *37.2* °C Level: *CONFORMS*	*6'00"*	*6'20"*	*6'55"*	*7'10"*	*7'40"*	*8'05"*
23-4-01 ~~*23-4-04*~~	*8:30*	Temp: _____ °C Level: *CONFORMS*	*6'50"*	*7'00"*	*7'30"*	*7'55"*	*8'15"*	*8'55"*
[initials] *23-4-01*	*14:00*	Temp: *37.3* °C Level: *CONFORMS*	*6'15"*	*6'45"*	*7'15"*	*7'30"*	*7'55"*	*8'15"*
24-4-01	*8:30*	Temp: *37.4* °C Level: *CONFORMS*	*6'10"*	*6'20"*	*6'50"*	*7'20"*	*7'45"*	*8'15"*
24-4-01	*12:00*	Temp: *37.4* °C Level: *CONFORMS*	*6'15"*	*6'45"*	*7'00"*	*7'15"*	*7'50"*	*8'20"*
		Temp: _____ °C Level: _____		[initials] *24/4/01*				

OPERATOR'S SIGNATURE: [signature]

VERIFIER'S SIGNATURE: [signature]

Checked by: [signature]

Product: SU10398	Lot: I83G02	Room: *72*	Page: *11* of *21*
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)		**DISTRIBUTION into CAPSULES**

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
24/4 01	*8*	**END OF DISTRIBUTION**	Date: *24-4-01* Time: *12:00*	[initials]	[initials]
24 /04 /01	*9*	**Controls on the finished product**		[initials]	[initials]
	9/1	Using the capsules sampled in point *5/1*, prepare and carry out the following samples:			
24 /04 /01	*9/2*	No.: *106* for section controls	No.: *106*		
	9/3	No.: *50* for chemical controls	No.: *50*		
	9/4	No.: *30* for dissolution and possible technological controls by SF/Pharmaceutical Controls	No.: *30*		
	9/5	[initials] *06/04/01* No.: *40 g* for bacterial loads	No.: *40 g*	[initials]	[initials]
	-	No.: ___ for [initials] *06/04/01*	No.: — [initials] *06/04/01*		
	9/6	*COMBINE ANY POSSIBLE EXCESS CAPSULES WITH THE BULK*			
24 /04 /01	*10*	**Section technological controls**			
	10/ 1	Perform the following section controls and report the data on the appropriate section regarding the FINISHED PRODUCT ☒ DURING PROCESSING ☐	Data reported on: FINISHED PRODUCT ☒ DURING PROCESSING ☐	[initials]	[initials]
	10/ 2	Uniformity of weight/average weight (SOP SF.CI 051)	☒		
	10/ 3	Disintegration (SOP SF.CI 015)	☒		

Product: SU10398 Lot: I83G02 Room: *72* Page: *12* of *21*

Pharmaceutical form: Capsule Dosage: 50 mg (as a free base)

DISTRIBUTION into CAPSULES

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
24 /04 /01	*11*	**Analytical controls on the finished product**			
	11/1	Send the above taken samples for the execution of the following controls and fill in the appropriate section regarding the: IN PROCESS ANALYTIC CONTROLS ☐ SENDING FOR FINISHED PRODUCT ANALYSIS ☒	Data reported on: IN PROCESS ANALYTIC CONTROLS ☐ SENDING FOR FINISHED PRODUCT ANALYSIS ☒	[initials]	[initials]
	11/2	Titer ☒	☒		
	11/3	Correlated substances ☒	☒		
24 /04 /01	–	Uniformity of content ☐	☐		
	11/4	Karl Fisher ☒	☒		
	11/5	Uniformity of weight ☒	☒		
	11/6	Dissolution ☒	☒		
	11/7	Bacterial load ☒	☒		
	11/8	Other: *HPLC IDENTITY* ☒	☒	[initials]	[initials]
	12	**Metal detector control**			
27 /04 /01	*12/1*	At the end of the distribution, pass the suitable capsules through the metal detector	Model: *LOCK METAL DETECTOR* ID number: *50/MT/04* Cleaning verification: *Yes* Operative parameters: *PRESET PROGRAM + VERIFICATION WITH STD SAMPLES – TEST OK.*	[initials]	[initials]
27 /04 /01	*12/2*	Verify the number of capsules discarded at the end of the operation	Discarded capsules: Gross: *70* g Tare: *20* g Net: *50* g Equal to *138/367* (number) capsules as calculated based on the average weight *0* [initials] *27/04/01*	[initials]	[initials]
	12/3	Take care to send the discarded capsules to be destroyed.	☒		

Checked by: [signature]

Product: SU10398	Lot: I83G02 Room: 72	Page: 13 of 21
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)	DISTRIBUTION into CAPSULES

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
27/04/01	13	**Processing yield controls**			
	13/1	At the end of the processing collect the capsules and place them in the following primary packaging: *DOUBLE PE BAGS + KRAFT BARREL*	Primary packaging used: *DOUBLE PE BAGS + KRAFT BARREL*	[initials]	[initials]
	13/2	Determine the quantity of product obtained in ponderal terms.	Ponderal yield: Gross: *6000* g Tare: *290* g Net: *5710* g (H)		
27/04/01	13/3	Calculate the numeric quantity of the obtained product:	Numeric yield:		
	13/4	Numeric yield = H / average weight(*) (*) Obtained by final controls	*5710* / *0.136 g* = No. *41985* (G)	[initials]	[initials]
	13/5	End of processing yield: (G / THEORETICAL(*)) * 100 (*) T from page 1	% Yield: *41985* / *48054* = *87.37* %		
24/04/2001	14	Calculate the mix quantity and residual shells and see to: SENDING THE MIX AND SHELLS TO BE DESTROYED ☒ SET ASIDE THE MIX ☐ NOTE:	Residual mix: Gross: *69.185 g*, Tare: *0.14 g*, Net: *69.171 g* / *69.045 g* Residual shells: Gross: *1.300 kg*, Tare: *0.290 kg*, Net: *1.010 kg* SENT TO BE DESTROYED ☒ SET ASIDE ☐	[initials]	[initials]

Product: SU10398	Lot: I83G02	Page: *14* of *21*
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)	

IN PROCESS ANALYTICAL CONTROLS

OPER. No.	DATE	SAMPLE No.	Numeric or ponderal quantity	CONTROL TYPE	LABORATORY	RESPONSE No. and DATE	OPERATOR	VERIFIER
				[initials] *06/04/01*				

TO SEND TO FINISHED PRODUCT ANALYSIS

DATE	Numeric or ponderal quantity	CONTROL TYPE	LABORATORY	RESPONSE No. and DATE	OPERATOR	VERIFIER
24-04-01	*50*	*CONTRAST CHEMICALS*	*AD6*	*No. 20011710 of 13 June 2001*	[initials]	[initials]
24-04-01	*30*	*DISSOLUTION / TECHNOLOGICAL*	*AD6*			
24-04-01	*40 g*	*MICROBIOLOGICAL*	*AD6*			

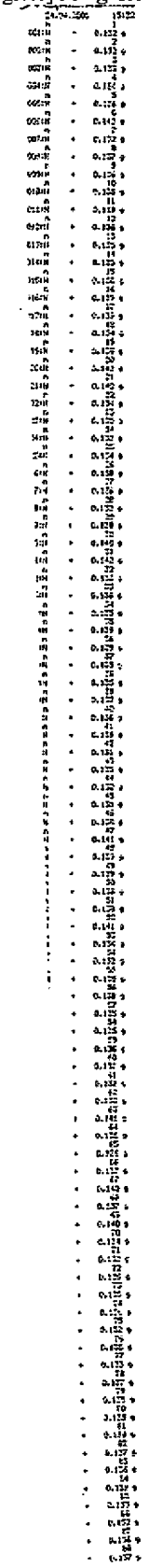
Product: SU10398	Lot: I83G02	Page: *15* of *21*
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)	

TECHNOLOGICAL CONTROLS ON THE FINISHED PRODUCT

DATE	CONTROL	LIMITS/REFERENCES	RESULT	OPERATOR	VERIFIER
24 /*04* /*01*	**WEIGHT** **SOP SF.CI 051**	Theoretical: *136* mg Minimum: *131* mg Maximum: *142* mg	Scale model: *SARTORIUS* ID number: *50 / BL /37* *SEE ATTACHED PRINTOUT*	[initials]	[initials] [initials]

PRODUCT SU10398
LOT I83K01
[illegible] *50mg CAPSULE*

[signature]



Product: SU10398 Lot: I83G02 Page: *16* of *21*

Pharmaceutical form: Capsule Dosage: 50 mg (as a free base)

TECHNOLOGICAL CONTROLS ON THE FINISHED PRODUCT

DATE	CONTROL	LIMITS/REFERENCES	RESULT	OPERATOR	VERIFIER
24 /04 /01	**AVERAGE WEIGHT** **SOP SF.CI 048**	[initials] *24-4-01* Theoretical: *137.26* ~~*136*~~ mg Minimum: *139* ~~*136.6 131*~~ mg [initials] *5/6/01* Maximum: ~~*143.93 626*~~ *140.6* mg	Average: *136.1* mg S.D.: *2.6* C.V.%: *1.91*		
24 /04 /01	**DISINTEGRATION** **SOP SF.CI 015**	Limit: *≤30'* Immersion fluid: *TDI WATER 37° C* Disks: Yes ☐ No ☒	Disintegrator: *SOTAX OT3* ID No.: *50 / DS /37* Immersion fluid: *TDI WATER 37° C* Temperature: *37.4* °C Liquid level: *CONFORMS* Disks: Yes ☐ No ☒ *6'15" 6'45" 7'10"* *7'55" 8'20" 8'45"*		
	LOSS OF WEIGHT **SOP SF.CI 029**	Limit: _____ Temperature: _____ °C Time: _____ [initials] *06/04/01*	Equipment: _____ ID No.: ____/____/____ Temperature: _____ °C Time: _____ minutes Loss of weight: _____ %		
	FRIABILITY **SOP SF.CI 025**	Quantity for the control: _____	Friabilimeter: _____ ID No.: ____/____/____ Initial weight: _____ g Final weight: _____ g Friability: _____ %		

Product: SU10398	Lot: I83G02	Page: *17* of *21*
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)	

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
	15	**Sorting the lot**			
27/04 /01	*15/1*	Proceed to the sorting of the sample as described in the following section. At the end of processing, collect a number of samples equal to 3% of the numeric yield of the lots at the end of processing, from various points in the bulk. Report the results on the corresponding page.	Quantity sampled: No. *1260* [illegible] *171 g* [initials]	[initials]	[initials]

Product: SU10398	Lot: I83G02	Page: *18* of *21*
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)	

SORTING of the SAMPLES from the PRODUCT OBTAINED at the END OF PROCESSING

PHARMACEUTICAL FORM: **CAPSULE**

QUANTITY OBTAINED: No. *41985* (A)

QUANTITY to be SORTED: No. *1260* (B) [Equal to 3% of A]

SORTING LIMITS -- PRIMARY DEFECTS: NOT MORE than THREE UNITS

APPEARANCE: _____

	DATE *27/4/01*	DATE	DATE	DATE	DATE	DATE
LIST OF PRIMARY DEFECTS	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES
CAPSULES BROKEN ON THE TIPS	*7*					
CAPSULES BROKEN ON THE BODY						
BODY IS VISUALIZED ON THE HEAD						
TOTAL	*7*					
LIST OF SECONDARY DEFECTS	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES
TOTAL						

NOTE: _____

Operator's signature	**Verifier's signature**	**Checked by:**
[signature]	[signature]	[signature]

APPEARANCE CONFORMITY

LOT CONFORMS for APPEARANCE ☐

LOT DOES NOT CONFORM for APPEARANCE go to UNIT SORTING ☒

SECTION CHIEF SIGNATURE: [signature]

Product: SU10398 Lot: I83G02 Page: *19* of *21*

Pharmaceutical form: Capsule Dosage: 50 mg (as a free base)

DATE	OPER. No.	OPERATION DESCRIPTION	PRODUCTION DATA	OPERATOR	VERIFIER
09/05/01	*15/2*	If the results of the sampling sorting are outside the set limits, proceed to unit sorting of the lot as described in the attached form.	☒	[initials]	[initials]
	15/3	At the end of the sorting operation, send the discarded product to be destroyed.	☒		
	16	**Counter sampling**			
24/04/01	*16/1*	Sample *100* (number) units and package them in: *P.E. BOTTLES*	Quantity sampled: No. *100* ☒	[initials]	[initials]
09/05/01	*17*	**Final lot yield control**			
	17/1	Proceed to the quantitative verification of the available product.	Available product Gross: *6.130* g Tare: *0.435* g Net: *5.695* g (U)	[initials]	[initials]
	17/2	Numeric yield = U / average weight(*) (*) Taken from the final controls	Numeric yield = *41.875 cps* (V) [illegible] [initials] 5.6.01		
10/05/01	*17/3*	% Yield = (V / THEORETICAL(*)) * 100 (*) T of page 1	*10-5-01* [initials] % Yield: ~~*87.66*~~ *87.14* (Z)	[initials]	[initials]
	18	**Deposit in the warehouse**			
10/05/01	*18/1*	Load the finished product and the counter sample into the SF/Warehouse, stocking them as: ~~*27*~~ TA [initials] *3/6/01*	☒	[initials]	[initials]

Pharmacia & Upjohn

Pharmaceutical Development / *Oral Solids and Warehousing*

Product: SU10398	Lot: I83G02	Room: 37	Attachment No.: *1* Page: *19*
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)		

UNIT SORTING

SORT TYPE: MANUAL ☒ WITH A SORTER ☐

SORTER MODEL: .....

CLEANING VERIFICATION: .....

	DATE *30/APR/01*	DATE *02/MAY/01*	DATE *07/MAY/01*	DATE *04/MAY/01*	DATE *02/MAY/01*	DATE *08//MAY/01*
LIST OF DEFECTS	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES	NO. OF PIECES
CAPSULES BROKEN ON THE TIPS	/	/	/	/	/	*6*
CAPSULES BROKEN ON THE BODY	/	/	/	/	*3*	
BODY IS VISUALIZED ON THE HEAD	/	/	/	/	*1*	*2*
CAPSULES CRUSHED AT TIPS	*66*	*58*	*65*	*70*	*59*	*60*
PARTIAL TOTAL	*66*	*58*	*65*	*70*	*63*	*68*

FINAL BALANCE

QUANTITY TO BE SORTED: ..... *41'985* ..... (K) *41'985*

TOTAL SORTED OUT TO BE DISCARDED: ..... ~~*3901*~~ ..... (Y) *397*

TOTAL SORTED INTO SELECTION: ..... ~~*41'5951*~~ ..... (X) *41'588** X= K-Y

10-05-01 [initials]

NOTE: K = Processing end yield – sample sorted out to be discarded

NOTES: **SEE OPERATION NUM 17/2*

Operator's signature: .....[signature].....

Verifier's signature: .....[signature].....

Edition No.: 7 of 10/05/99
Substitutes edition No.: 6 of 03/11/97

Checked by: _____[signature]_____

Product: SU10398 Lot: I83G02

Pharmaceutical form: Capsule Dosage: 50 mg (as a free base)

DATE	OPERATION No.	NOTES [initials] *14/05/01*	OPERATOR	VERIFIER
14/05/01	*7/2 and 7/3*	*~~THE GAPS BETWEEN THE INTERMEDIATE~~*		
		AMONG THE CONTROLS IN WEIGHT		
		GREATER THAN THAT PROVIDED FOR OCCURRED WHERE THE		
		PRODUCTION STOPPED DUE TO THE NEED TO CLEAN THE MACHINE		
		(LOAD HOPPER, DISPENSER, BASIN, ETC.) AND CLEAN OUT THE MIX		
		WHICH WAS PARTICULARLY ADHESIVE. AS THESE STOPS WERE		
		FREQUENT AND PROBLEMATIC THE RESTORATION DECIDED TO		
		RECORD IT IN THE FINAL NOTES. [initials] *14 MAY 2001*		
14/05/01	*7/2*	*THE OUT OF LIMIT WEIGHT REVEALED IN THE WEIGHT CONTROL*		
		OF: 19 APRIL 2001 AT 15:49 WAS "CORRECTED" BY WEIGHING THE		
		UNIT OF THE CAPSULES RELATIVE TO THE CORRESPONDING		
		PRODUCTION PERIOD. IN PROCESS, CONSIDERING THE PROBLEMS		
		OF THE PROCESS, THE CAPSULES OF VARIOUS PRODUCTION		
		BATCHES WERE SEPARATELY COLLECTED (BETWEEN THE TWO		
		WEIGHT CONTROLS) AND COMBINED WITH THE BULK ONLY AFTER A		
		FINAL CONTROL WAS PERFORMED. [initials] *14 MAY 2001*		
	17/2	*For the calculation of the yield an average weight equal to 136mg was used*		
		rather than 136.1 (the operator incorrectly rounded off the average weight)		
		[signature] *5 June 2001*		

Product: SU10398	Lot: I83G02	Page *21* of *21*
Pharmaceutical form: Capsule	Dosage: 50 mg (as a free base)	

LOT APPROVAL

OPERATIVE VERIFICATION of the "ORAL SOLIDS" SECTION

NOTES: _____

SIGNATURE: [signature] DATE: *14/05/01*

CHIEF of "ORAL SOLIDS and WAREHOUSING" APPROVAL

RESULTS: APPROVED ☒ REJECTED ☐

NOTES: _____

SIGNATURE: [signature] DATE: *15/6/01*

USE AUTHORIZATION OF THE CHIEF of "Q.C./PHARMACEUTICAL CONTROLS"

RESULTS: APPROVED ☒ REJECTED ☐

NOTES: _____

SIGNATURE: [signature] DATE: *15/6/01*

SF/ORAL SOLIDS

PRODUCT *SU10398 CPS 50 mg (AS FREE BASE)*

LOT *I83K01*

PREPARATION DATE *04/01*

ATTACHED INDEXES

1.	☐	ACTIVE PRINCIPLE ANALYSIS REPORT
2.	☐	IN PROCESS ANALYTIC CONTROLS REPORT
3.	☐	PROCESS WATER REPORT
4.	☒	ENVIRONMENTAL PARAMETER MONITORING
5.	☒	RAW MATERIALS/PACKAGING MATERIALS REQUESTS
6.	☒	FINISHED PRODUCT ANALYSIS REPORT
7.	☐	BACTERIAL LOAD REPORT
8.	☒	FINISHED PRODUCT DELIVERY FORM
9.	☒	ANALYSES CERTIFICATE
10.	☒	RAW DATA, in process weight controls.
11.	☒	*SCHEDULED DEVIATION 14/01:ONLY INTERMEDIATE CLEANING BETWEEN SU* [illegible] *and SU10398*
12.	☐	
13.	☐	
14.	☐	

NOTES: _____

Pharmacia&Upjohn
Pharmacia & Upjohn S.p.A.
Viale Pasteur , 10
20014 Nerviano (MI)
Italy

[initials] *LOT I83G02*

24.04.2001		08:40
n°		1
001:N	+	0.138 g
n		2
002:N	+	0.140 g
n		3
003:N	+	0.140 g
n		4
004:N	+	0.141 g
n		5
005:N	+	0.141 g
n		6
006:N	+	0.141 g
n		7
007:N	+	0.137 g
n		8
008:N	+	0.139 g
n		9
009:N	+	0.142 g
n		10
010:N	+	0.139 g
n		11
011:N	+	0.141 g
n		12
012:N	+	0.141 g
n		13
013:N	+	0.138 g
n		14
014:N	+	0.138 g
n		15
015:N	+	0.142 g
n		16
016:N	+	0.138 g
n		17
017:N	+	0.140 g
n		18
018:N	+	0.140 g
n		19
019:N	+	0.137 g
n		20
020:N	+	0.138 g

n	20
x̄	0.1396 g
s	0.0016 g
srel	1.15 %
Ex	2.791 g
min	0.137 g
max	0.142 g
Diff	0.005 g

24.04.2001		08:
n		1
001:N	+	0.139 g
n		2
002:N	+	0.138 g
n		3
003:N	+	0.139
n		4
004:N	+	0.135
n		5
005:N	+	0.137
n		6
006:N	+	0.138
n		7
007:N	+	0.138
n		8
008:N	+	0.138
n		9
009:N	+	0.139
n		10
010:N	+	0.138
n		11
011:N	+	0.135
n		12
012:N	+	0.139
n		13
013:N	+	0.138
n		14
014:N	+	0.135
n		15
015:N	+	0.13
n		16
016:N	+	0.13
n		17
017:N	+	0.13
n		18
018:N	+	0.13
n		19
019:N	+	0.13
n		2
020:N	+	0.13

n	2
x̄	0.13
s	0.00
srel	1.(
Ex	2.7
min	0.1
max	0.1
Diff	0.0

LOT [illegible]

	24.04.2001	09:30
n		1
001:N	+	0.136 g
n		2
002:N	+	0.137 g
n		3
003:N	+	0.137 g
n		4
004:N	+	0.136 g
n		5
005:N	+	0.134 g
n		6
006:N	+	0.134 g
n		7
007:N	+	0.135 g
n		8
008:N	+	0.135 g
n		9
009:N	+	0.134 g
n		10
010:N	+	0.136 g
n		11
011:N	+	0.135 g
n		12
012:N	+	0.137 g
n		13
013:N	+	0.139 g
n		14
014:N	+	0.135 g
n		15
015:N	+	0.133 g
n		16
016:N	+	0.132 g
n		17
017:N	+	0.133 g
n		18
018:N	+	0.135 g
n		19
019:N	+	0.138 g
n		20
020:N	+	0.133 g

n	20
x̄	0.1352 g
s	0.0018 g
srel	1.33 %
Σx	2.704 g
min	0.132 g
max	0.139 g
Diff	0.007 g

	24.04.2001	10:0
n		1
001:N	+	1.364 g
n		2
002:N	+	0.135 g
n		3
003:N	+	0.135 g
n		4
004:N	+	0.136 g
n		5
005:N	+	0.134 g
n		6
006:N	+	0.136 g
n		7
007:N	+	0.138 g
n		8
008:N	+	0.136 g
n		9
009:N	+	0.135 g
n		10
010:N	+	0.137 g
n		11
011:N	+	0.135 g
n		12
012:N	+	0.138 g
n		13
013:N	+	0.136 g
n		14
014:N	+	0.135 g
n		15
015:N	+	0.139 g
n		16
016:N	+	0.134 g
n		17
017:N	+	0.137
n		18
018:N	+	0.134
n		19
019:N	+	0.137
n		20
020:N	+	0.135

[illegible]

n	20
x̄	0.1973
s	0.2746
srel	139.18
Σx	3.946
min	0.134
max	1.364
Diff	1.230

~~46~~ LOT 78360

23.04.2001 08:44

n			1
001:N	+	0.138	g
n			2
002:N	+	0.133	g
n			3
003:N	+	0.137	g
n			4
004:N	+	0.139	g
n			5
005:N	+	0.137	g
n			6
006:N	+	0.137	g
n			7
007:N	+	0.137	g
n			8
008:N	+	0.140	g
n			9
009:N	+	0.137	g
n			10
010:N	+	0.132	g
n			11
011:N	+	0.137	g
n			12
012:N	+	0.138	g
n			13
013:N	+	0.137	g
n			14
014:N	+	0.138	g
n			15
015:N	+	0.135	g
n			16
016:N	+	0.138	g
n			17
017:N	+	0.136	g
n			18
018:N	+	0.136	g
n			19
019:N	+	0.136	g
n			20
020:N	+	0.137	g

n	20
x̄	0.1368 g
s	0.0018 g
srel	1.32 %
Σx	2.735 g
min	0.132 g
max	0.140 g
Diff	0.008 g

23.04.2001 09:

n			1
001:N	+	0.139	g
n			2
002:N	+	0.138	g
n			3
003:N	+	0.141	g
n			4
004:N	+	0.137	g
n			5
005:N	+	0.133	g
n			6
006:N	+	0.139	g
n			7
007:N	+	0.137	g
n			8
008:N	+	0.136	g
n			9
009:N	+	0.136	g
n			10
010:N	+	0.138	g
n			11
011:N	+	0.140	g
n			12
012:N	+	0.135	g
n			13
013:N	+	0.138	g
n			14
014:N	+	0.138	g
n			15
015:N	+	0.138	g
n			16
016:N	+	0.136	g
n			17
017:N	+	0.137	g
n			18
018:N	+	0.13	g
n			1
019:N	+	0.13	g
n			2
020:N	+	0.13	g

n	1
x̄	0.138
s	0.00
srel	1.
Σx	2.7
min	0.1
max	0.1
Diff	0.0

LOT 28360

20-Apr-2001 7:51:50

	20.04.2001	07:47
n		1
001:N	+	0.135 g
n		2
002:N	+	0.136 g
n		3
003:N	+	0.137 g
n		4
004:N	+	0.140 g
n		5
005:N	+	0.139 g
n		6
006:N	+	0.139 g
n		7
007:N	+	0.135 g
n		8
008:N	+	0.138 g
n		9
009:N	+	0.142 g
n		10
010:N	+	0.138 g
n		11
011:N	+	0.134 g
n		12
012:N	+	0.141 g
n		13
013:N	+	0.136 g
n		14
014:N	+	0.135 g
n		15
015:N	+	0.139 g
n		16
016:N	+	0.137 g
n		17
017:N	+	0.136 g
n		18
018:N	+	0.135 g
n		19
019:N	+	0.142 g
n		20
020:N	+	0.136 g

n	20
x̄	0.1376 g
s	0.0023 g
srel	1.67 %
Σx	2.752 g
Min	0.134 g
Max	0.142 g
Diff	0.008 g

	20.04.2001	08:47
n		1
001:N	+	0.139 g
n		2
002:N	+	0.141 g
n		3
003:N	+	0.143 g
n		4
004:N	+	0.138 g
n		5
005:N	+	0.139 g
n		6
006:N	+	0.143 g
n		7
007:N	+	0.139 g
n		8
008:N	+	0.140 g
n		9
009:N	+	0.140 g
n		10
010:N	+	0.137 g
n		11
011:N	+	0.138 g
n		12
012:N	+	0.141 g
n		13
013:N	+	0.141 g
n		14
014:N	+	0.141 g
n		15
015:N	+	0.137 g
n		16
016:N	+	0.141 g
n		17
017:N	+	0.139 g
n		18
018:N	+	0.140 g
n		19
019:N	+	0.141 g
n		20
020:N	+	0.142 g

n	20
x̄	0.1400 g
s	0.0018 g
srel	1.28 %
Σx	2.799 g
Min	0.137 g
Max	0.143 g
Diff	0.006 g

LOT

19-Apr-2001 21:00:05

	19.04.2001	08:03
n		1
0001H	+	0.134 g
n		2
0002H	+	0.140 g
n		3
0003H	+	0.137 g
n		4
0004H	+	0.137 g
n		5
0005H	+	0.132 g
n		6
0006H	+	0.133 g
n		7
0007H	+	0.136 g
n		8
0008H	+	0.134 g
n		9
0009H	+	0.126 g
n		10
0010H	+	0.135 g
n		11
0011H	+	0.132 g
n		12
0012H	+	0.134 g
n		13
0013H	+	0.135 g
n		14
0014H	+	0.136 g
n		15
0015H	+	0.136 g
n		16
0016H	+	0.135 g
n		17
0017H	+	0.136 g
n		18
0018H	+	0.134 g
n		19
0019H	+	0.134 g
n		20
0020H	+	0.133 g

n	20
x	0.1364 g
s	0.0019 g
srel	1.39 %
Xv	2.755 g
min	0.133 g
max	0.140 g
Diff	0.007 g

	19.04.2001	08:26
n		1
0001H	+	0.135 g
n		2
0002H	+	0.138 g
n		3
0003H	+	0.137 g
n		4
0004H	+	0.140 g
n		5
0005H	+	0.136 g
n		6
0006H	+	0.139 g
n		7
0007H	+	0.134 g
n		8
0008H	+	0.137 g
n		9
0009H	+	0.139 g
n		10
0010H	+	0.139 g
n		11
0011H	+	0.136 g
n		12
0012H	+	0.137 g
n		13
0013H	+	0.139 g
n		14
0014H	+	0.136 g
n		15
0015H	+	0.141 g
n		16
0016H	+	0.136 g
n		17
0017H	+	0.139 g
n		18
0018H	+	0.137 g
n		19
0019H	+	0.139 g
n		20
0020H	+	0.137 g

n	20
x	0.1373 g
s	0.0015 g
srel	1.11 %
Xv	2.745 g
min	0.135 g
max	0.141 g
Diff	0.007 g

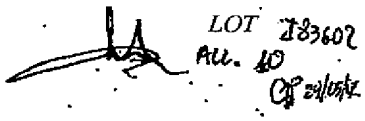
	19.04.2001	09:5
n		1
0001H	+	0.135 g
n		2
0002H	+	0.137 g
n		3
0003H	+	0.133 g
n		4
0004H	+	0.138 g
n		5
0005H	+	0.141 g
n		6
0006H	+	0.132 g
n		7
0007H	+	0.136 g
n		8
0008H	+	0.135 g
n		9
0009H	+	0.137 g
n		10
0010H	+	0.138 g
n		11
0011H	-	0.141 g
n		12
0012H	+	0.134 g
n		13
0013H	-	0.136 g
n		14
0014H	+	0.132 g
n		15
0015H	+	0.133 g
n		16
0016H	+	0.132 g
n		17
0017H	+	0.134 g
n		18
0018H	+	0.141 g
n		19
0019H	+	0.135 g
n		20
0020H	+	0.139 g

n	20
x	0.1378 g
s	0.0031 g
srel	2.26 %
Xv	2.756 g
min	0.132 g
max	0.141 g
Diff	0.008 g

18.04.2001 15:07

n		1	
ART.ID			9
002:N	+	0.136	g
n		2	
003:N	+	0.137	g
n		3	
004:N	+	0.140	g
n		4	
005:N	+	0.134	g
n		5	
006:N	+	0.137	g
n		6	
007:N	+	0.135	g
n		7	
008:N	+	0.138	g
n		8	
009:N	+	0.138	g
n		9	
010:N	+	0.138	g
n		10	
011:N	+	0.135	g
n		11	
012:N	+	0.133	g
n		12	
013:N	+	0.138	g
n		13	
014:N	+	0.135	g
n		14	
015:N	+	0.134	g
n		15	
016:N	+	0.134	g
n		16	
017:N	+	0.137	g
n		17	
018:N	+	0.136	g
n		18	
019:N	+	0.139	g
n		19	
020:N	+	0.136	g
n		20	
021:N	+	0.136	g

n	21	
x̄	0.1363	g
s	0.0018	g
srel	1.32	%
Σx	2.863	g



18-Apr-2001 14:13:12

	18.04.2001		14:07
	n		1
001:	N	+	0.136 g
	n		2
002:	N	+	0.135 g
	n		3
003:	N	+	0.136 g
	n		4
004:	N	+	0.135 g
	n		5
005:	N	+	0.135 g
	n		6
006:	N	+	0.138 g
	n		7
007:	N	+	0.137 g
	n		8
008:	N	+	0.133 g
	n		9
009:	N	+	0.137 g
	n		10
010:	N	+	0.135 g
	n		11
011:	N	+	0.138 g
	n		12
012:	N	+	0.133 g
	n		13
013:	N	+	0.135 g
	n		14
014:	N	+	0.138 g
	n		15
015:	N	+	0.137 g
	n		16
016:	N	+	0.135 g
	n		17
017:	N	+	0.136 g
	n		18
018:	N	+	0.134 g
	n		19
019:	N	+	0.134 g
	n		20
020:	N	+	0.136 g
n			20
x̄			0.1357 g
s			0.0015 g
srel			1.11 %
Σx			2.713 g
min			0.133 g
max			0.138 g
Diff			0.005 g

LOT 283602

18.04.2001 14:28

	n		1
001:	N	+	0.136 g
	n		2
002:	N	+	0.134 g
	n		3
003:	N	+	0.135 g
	n		4
004:	N	+	0.135 g
	n		5
005:	N	+	0.139 g
	n		6
006:	N	+	0.135 g
	n		7
007:	N	+	0.135 g
	n		8
008:	N	+	0.136 g
	n		9
009:	N	+	0.139 g
	n		10
010:	N	+	0.134 g
	n		11
011:	N	+	0.136 g
	n		12
012:	N	+	0.134 g
	n		13
013:	N	+	0.134 g
	n		14
014:	N	+	0.137 g
	n		15
015:	N	+	0.135 g
	n		16
016:	N	+	0.138 g
	n		17
017:	N	+	0.132 g
	n		18
018:	N	+	0.134 g
	n		19
019:	N	+	0.137 g
	n		20
020:	N	+	0.134 g

n	20
$\bar{x}$	0.1355 g
s	0.0018 g
srel	1.33 %
Σx	2.709 g
min	0.132 g
max	0.139 g
Diff	0.007 g

LOT I83402

19.04.2001 15:4

n			1
001:N	+	0.142	g
n			2
002:N	+	0.141	g
n			3
003:N	+	0.136	g
n			4
004:N	+	0.140	g
n			5
005:N	+	0.138	g
n			6
006:N	+	0.142	g
n			7
007:N	+	0.140	g
n			8
008:N	+	0.138	g
n			9
009:N	+	0.118	g
n			10
010:N	+	0.136	g
n			11
011:N	+	0.136	g
n			12
012:N	+	0.142	g
n			13
013:N	+	0.140	g
n			14
014:N	+	0.138	g
n			15
015:N	+	0.135	g
n			16
016:N	+	0.139	g
n			17
017:N	+	0.140	g
n			18
018:N	+	0.141	g
n			19
019:N	+	0.143	g
n			20
020:N	+	0.136	g

n	20	
x̄	0.1381	g
s	0.0053	g
srel	3.84	%
Σx	2.761	g
min	0.118	g
max	0.143	g
Diff	0.025	g

20-Apr-2001 [redacted]

LOT 253 602
ATTACHMENT 4 [initials] *29 MAY 2002*
NONE OF THE [illegible] *POSSIBLE RISKS OF CONTAMINATION OF THE* [illegible]
SEE NOTE [illegible] [initials] *29 MAY 2002*

29-05-02 20:46 - 1- fabIC MAN-CRAL

C4 ALLARM SYSTEM SUMMARY

Point/Acknowledge Event Report with following specifications:

Start Date/Time : 12-04-01 08:00 Stop Date/Time : 10-05-01 17:00
Time Range : --- days --- hours

Selected Events : Point Events

	Point Keyname	Point Descriptor
1	650-33.0-CDICAMAIPHTH3	UNID.RIPR.COUNTER H3 LIMITE (25MH
2	650-33.0-CDICAMAIPHTH4	UNID.RIPR.COUNTER H4 LIMITE (25MH
3	650-33.0-CDICAMAIPHTH5	UNID.RIPR.COUNTER H5 LIMITE (25MH
4	650-33.0-CDICAMAIPHTH6	UNID.RIPR.COUNTER H6 LIMITE (25MH
5	650-33.0-CDICAMAIPHTH7	UNID.RIPR.COUNTER H7 LIMITE (25MH
6	650-33.0-PILOCALE0085	PRES.LOC.085 LIMITE (-0.8/0.01
7	650-33.0-PILOCALE0084	PRES.LOC.084 LIMITE (-0.8/0.01
8	650-33.0-PILOCALE0083	PRES.LOC.083 LIMITE (-0.8/0.01
9	650-33.0-PILOCALE0080	PRES.LOC.080 LIMITE (-0.8/0.01
10	650-33.0-PILOCALE0081	PRES.LOC.081 LIMITE (-0.8/0.01
11	650-33.0-PILOCALE0082	PRES.LOC.082 LIMITE (-0.8/0.01
12	650-33.0-PILOCALE0079	PRES.LOC.079 LIMITE (-0.8/0.01
13	650-33.0-PILOCALE0078	PRES.LOC.078 LIMITE (-0.8/0.01
14	650-33.0-PILOCALE0077	PRES.LOC.077 LIMITE (-0.8/0.01
15	650-33.0-PILOCALE0076	PRESSIONE LOCALE 076 LIMITE(-0.8/0.01
16	650-33.0-PILOCALE0075	PRESSIONE LOCALE 075 LIMITE(-0.8/0.01
17	650-33.0-PILOCALE0074	PRESSIONE LOCALE 074 LIMITE(-0.8/0.01
18	650-33.0-PILOCALE0073	PRESSIONE LOCALE 073 LIMITE(-0.8/0.01
19	650-33.0-PILOCALE0072	PRES.LOC.072 LIMITE (-0.8/0.01
20	650-33.0-PILOCALE0071	PRES.LOC.071 LIMITE (-0.8/0.01
21	650-33.0-PILOCALE0070	PRES.LOC.070 LIMITE (-0.8/0.01
22	650-33.0-PILOCALE0069	PRES.LOC.069 LIMITE (-0.8/0.01
23	650-33.0-PILOCALE0068	PRES.LOC.068 LIMITE (-0.8/0.01
24	650-33.0-PILOCALE0067	PRES.LOC.067 LIMITE (-0.8/0.01
25	650-33.0-PILOCALE0066	PRES.LOC.066 LIMITE (-0.8/0.01

LOG TIME	KEYNAME SYSTEM ALARM TEXT POINTDESCRIPTION	VALUE OPERATOR	ENG.UNIT PREFIX
02-05-01 10:45:02	650-33.0-PILOCALE0073 PRES.LOC.073 LIMITE (-0.8/0.01	-1.19	MLB alm min
02-05-01 10:50:19	650-33.0-PILOCALE0073 PRES.LOC.073 LIMITE (-0.8/0.01	-0.76	MLB rel norm
02-05-01 12:45:14	650-33.0-CDICAMAIPHTH6 UNID.RIPR.COUNTER H6 LIMITE (25MH	60.0	MH alm max

29-05-02 20:46 - 2- fabIC MAN-CRAL

C4 ALLARM SYSTEM SUMMARY

LOG TIME	KEYNAME SYSTEM ALARM TEXT POINTDESCRIPTION	VALUE OPERATOR	ENG.UNIT PREFIX
02-05-01 15:11:11	650-33.0-CDICAMAIPHTH6 UNID.RIPR.COUNTER H6 LIMITE (25MH	59.0	MH rel norm
03-05-01 09:40:42	650-33.0-PILOCALE0037 PRES.LOC.037 LIMITE (-0.8/0.01	-0.49	MLB alm min
03-05-01 09:40:50	650-33.0-PILOCALE0037 PRES.LOC.037 LIMITE (-0.8/0.01	-0.22	MLB rel norm
04-05-01 08:59:56	650-33.0-PILOCALE0037 PRES.LOC.037 LIMITE (-0.8/0.01	-0.50	MLB alm min
04-05-01 09:04:05	650-33.0-PILOCALE0037 PRES.LOC.037 LIMITE (-0.8/0.01	-0.30	MLB rel norm
04-05-01 10:47:23	650-33.0-PILOCALE0073 PRES.LOC.073 LIMITE (-0.8/0.01	0.11	MLB alm max
04-05-01 10:51:01	650-33.0-PILOCALE0073 PRES.LOC.073 LIMITE (-0.8/0.01	-0.02	MLB rel norm
04-05-01 15:24:25	650-33.0-PILOCALE0073 PRES.LOC.073 LIMITE (-0.8/0.01	-1.16	MLB alm min
04-05-01 15:34:24	650-33.0-PILOCALE0073 PRES.LOC.073 LIMITE (-0.8/0.01	0.09	MLB alm max
04-05-01 15:35:27	650-33.0-PILOCALE0073 PRES.LOC.073 LIMITE (-0.8/0.01	-0.01	MLB rel norm
04-05-01 15:36:27	650-33.0-PILOCALE0073 PRES.LOC.073 LIMITE (-0.8/0.01	-0.79	MLB rel norm
07-05-01 09:02:49	650-33.0-PILOCALE0037 PRES.LOC.037 LIMITE (-0.8/0.01	-0.49	MLB alm min
07-05-01 09:06:01	650-33.0-PILOCALE0037 PRES.LOC.037 LIMITE (-0.8/0.01	-0.26	MLB rel norm

29-05-02 20:46 - 3- fabIC MAN-CRAL

C4 ALLARM SYSTEM SUMMARY

LOG TIME	KEYNAME SYSTEM ALARM TEXT POINTDESCRIPTION	VALUE OPERATOR	ENG.UNIT PREFIX
07-05-01 10:04:55	650-33.0-PILOCALE0037 PRES.LOC.037 LIMITE (-0.8/0.01	-0.29	MLB alm min
07-05-01 10:06:52	650-33.0-PILOCALE0037 PRES.LOC.037 LIMITE (-0.8/0.01	-0.30	MLB rel norm

A total of 18 records were found for "Historical Activity Inquiry".

END OF REPORT

LOT I83G02
ATTACHMENT 11 [initials] *24 MAY 2002*

SCHEDULED DEVIATION REQUEST

SECTION: Oral Solid Products R&D	**No.:** *14/01* (as performed by the QA/Quality Systems Section)

DOCUMENT NUMBER AND TITLE:
SF.TD 069 Vers. 2: Cleaning of the equipment for the preparation of oral solids pharmaceutical products.

PRODUCT/MATERIAL/LOT:	ACTIVITY:
SU010398 Lot (A) 5975-MTM-0002 (malate salt of SU011248)	Production of granulated lot I83K01 Production of capsules lot I83G02

DESCRIPTION OF PROPOSED DEVIATION:
Execution of intermediary cleaning of the equipment previously used for the processing of SU011248 (lots 182K01 and 182G02). The cleaning of the equipment by vacuum and the cleaning of the fluid bed granulator is to be carried out with TDI Water. Then we will proceed to sampling the equipment used in the points indicated in the communication of 2 April (see Attachment 1) solely for informative purposes.

MOTIVATION:
The technical rationale for the deviation is provided in the attached documentation:
Attachment 2: Memorandum by Sardar Ali (9/02/01)
Attachment 3: Communication by David Hahn (14/02/01)

SIGNATURE/DATE [signature] *06/04/01*

For a process, provide the start and end dates of the process in advance:

17-20 April 2001 *09-30 April 2001* [signature] *06 April 2001*

DEVIATION APPROVAL

SECTION CHIEF:	**QA/QUALITY SYSTEMS:**
[signature]	[signature] *April 6th, 2001*

Author: Paolo Gatti at itnerpo4
Date: 4/2/01 4:55 PM
Priority: Normal
CC: Rosaria Mariani, Luciano Gambini, Paolo DellaVedova, Mauro Ulivieri, Donata Giudici at ITNERPO1
TO: Irma Facchetti

Subject: Re[3]: Intermediate cleaning between the manufacturing of SU011248 and SU010 capsules

Hi Everyone,

Luciano and I have defined which points to sample and analyze in the machines used for the processing of SU11248 cleaned with intermediate cleaning prior to working on SU10398.

It has been decided that one point per machine will be sampled, considering that the result with the greatest residue per unit is superficial after the greater cleaning performed prior to the first lot of SU11248 capsules.

In absolute, the following points will be sampled and analyzed (here is the detailed list for Giorgio who will prepare the swabs accordingly):

Zanasi capsule sealer	Hopper base	(OP/05/1P)
Viani Oscillating Granulator	Rear rotor housing	(GS/03/1P)
Glatt 5 Fluid bed dryer	Spy zone	(LF/02/1P)
Diosna Speed Granulator	Crusher	
Pellegrini V Mixer	Bottom	(MS/27/2P)

I spoke with Giorgio and tomorrow he will take the samples and send the swabs to Rita.

The list of sample points will be inserted into the scheduled deviation that will be drawn up to support the "in campaign" processing of the two products which have different instructions (11248 and 10398).
I will meet tomorrow morning with Luciano and Donata about this.

Bye everyone.

Paolo

_____ Reply Separator _____
Subject: Re[2]: Cleaning intermedio fra mfg capsule SU011248 ed SU010
Author: Irma Facchetti at itnerpo4
Date: 02/04/01 14.21

Paolo,
I'm sorry for the lack of understanding about the deviation.

When operation methods different from those described in a SOP are adopted (such as in this case), it is necessary to follow the procedure regarding the deviations.

Bye,
Irma

_____ Reply Separator _____
Subject: Re: Cleaning intermedio fra mfg capsule SU011248 ed SU010398
Author: Paolo Gatti at itnerpo4
Date: 4/2/01 1:09 PM

Irma,
With regard to the scheduled deviation, I would ask that you forward Sugen's memo and Dave's email to me so that I can get things going as soon as possible with Donata. Only one thing is not clear. It is the first time I have heard about the need for scheduled deviation even though it's been at least a month that we've known we would have only done one intermediate cleaning. I have nothing against doing these documents, and I'm absolutely not arguing, but sometimes it would be better if things were defined a little bit in advance.

In my opinion, the same is true for the sampling and analyses. Tomorrow Giorgio will sample the machines in all the points indicated

by the respective cleaning SOP (I think we all agree on this), so that the analyses can be performed. However the execution time is also linked to the availability of Rita's group, as well as to the decision regarding which points are effectively to be analyzed.
I repeat my warning (and I think Rita would agree...) that it is not logical to analyze all the points if they are not strictly necessary according to the rationale with which this verification is to be handled, and which I will evaluate first with Paolo DellaVedova to be sure I have properly understood.

Thank you for your quick update after our chat this morning.

Bye,
Paolo

Reply Separator

Subject: Cleaning intermedio fra mfg capsule SU011248 ed SU010398
Author: Irma Facchetti at itnerpo4
Date: 02/04/01 12.49

Paolo,

Speaking as QA, I ask that you:

-open a scheduled deviation request and attach the documents detailing the rationale. There is a Memo by Sugen and an E-mail by Dave which will be formalized into a Memo shortly.

With regard to the sampling requested by Shahe:

-within the bounds of the cleaning procedure, for an intermediate type cleaning, no sampling is provided for. The choice of critical points to be examined will be defined with Paolo Della Vedova.

-it would be advisable to carry out these doses within the shortest possible time provided that there is no data or valid rationale which would allow claims to be made regarding the stability of the product under the conservation conditions and time periods that are to be defined.

Best regards
Irma

Attachment 3a
DEVIATION REQUEST
14/01

SUGEN

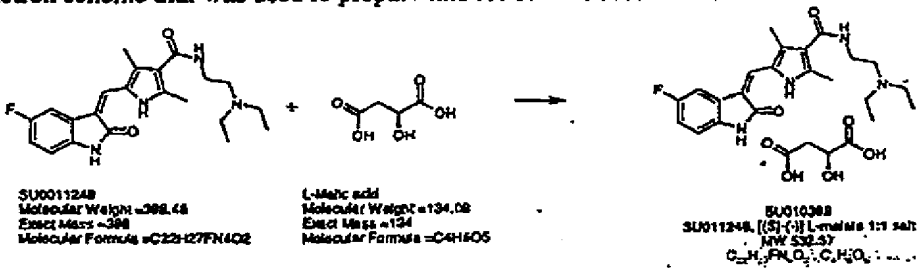
Memorandum

To:	Sardar Ali	**From:**	Peter Giannousis
Dept:		**Dept:**	PCPD – Analy & Chem. Dev.
Loc./Tel.		**Loc./Tel.**	B2-2403 ; X3705
Cc:	Arun Koparkar, James Gage, Bhavesh Patel	**Date:**	09-Feb-01
Subject:	**Genealogy of SU010398 lot (A)5975-MTM-0002**		

Dear Sardar,

Per your request, the following is a summary of the genealogy of SU010398 lot (A)5975-MTM-0002.

The reaction scheme that was used to prepare this lot of SU010398 from SU011248 is:



In fact SU011248 lot (A2)5953-TJF-0003 was used as starting material to prepare SU010398 lot (A)5975-MTM-0002. SU010398 is the L-malate salt of SU011248, and as such contains about 75% of SU011248 by weight.

The impurities in SU011248 lot (A2)5953-TJF-0003 were higher than those in the previous lots of SU011248 that were tested in GLP toxicological studies. Therefore SU011248 lot (A2)5953-TJF-0003 was qualified for human use by repeating the 2-week tox study. A memo was issued in early January from Toxicology, certifying that there were no significant differences seen in the tox studies with the new lot versus previous lots of SU011248.

The impurities in SU010398 lot (A)5975-MTM-0002 were found to be similar or lower than those in SU011248 lot (A2)5953-TJF-0003. In fact this lot of SU010398 is being used in 3-month GLP tox studies, with results available in May-June 2001.

Based on these facts, it would be expected that there should be no contamination issues in sequential capsule manufacture, as long as the bulk of the SU011248 and the excipients are removed from the equipment. In other words, one would expect that the API impurities would be comparable, and the amount of freebase left in the equipment should be much less than weighing errors of the L-malate salt.

Peter Giannousis

Author: David A Hahn at ITNERPO5
Date: 2/14/01 4:39 PM
Normal
TO: bhavesh-patel@sugen.com at SUGEN, chandu-hegde@sugen.com at SUGEN, peter-giannousis@sugen.com at SUGEN, sardar-ali@sugen.com at SUGEN
CC: Marco Adami at ITNERPO4, Marina Baldi at ITNERPO4, Irma Facchetti at ITNERPO4, Paolo Gatti at ITNERPO4, Rosaria Mariani at ITNERPO4, Mauro Ulivieri at ITNERPO4, Luciano Gambini at ITNERPO4
Subject: Re: Sequential capsule manufacturing from free base and L-ma
---------- Message Contents

Sardar,

Here is the general logic that I have in mind. This could be developed in more depth, or in a different way (to the extent allowed by the data). Please let me know what you think.

(1) Solubility and rotating disk dissolution rate data indicate that both the free base and the malate salt have solubility "more than sufficient to prevent solubility from being a limiting factor in the bioavailability," according to Study Report a0089789. Thus, a small amount of one material in the other would not be expected to have any impact on biological performance.

(2) Paolo estimates that after the proposed dry cleaning that the amount of granulation remaining would certainly be less than 10 grams (probably much less). If as much as 10 g remained, this would amount to less than 0.2% of a 5.3 kg granulation batch (using 3.5 kg FBE of API). Given the similar dissolution behaviors, the presence of 0.2% of a granulation of one salt in a granulation of the other would not be expected to influence the biological performance.

(3) Because the process uses wet granulation, the granulated material of which traces would remain on the surfaces of the equipment would likely be representative of the previous granulation, and would likely be incorporated homogeneously into the subsequent granulation. Thus, the presence of a small amount of material from the previous granulation would not be expected to significantly alter the chemical or physical properties of the subsequent granulation.

(4) And I understand that Peter is developing a rationale for safety of the impurity levels based on the geneological relationship between the batches involved and based on the fact that the qualified impurities levels would allow use of either batch in humans.

Please let me know if you have any comments, questions or concerns.

Ciao,

Dave

Reply Separator

Subject: Sequential capsule manufacturing from free base and L-malate
Author: Sardar Ali <sardar-ali@sugen.com> at SMTP-KZO
Date: 2/12/01 5:37 PM

Dear Dr. Hahn,

Reference to our meeting in Nerviano (during my visit) with Irma, and Rita dated 1/25/01, we had discussed the impact of sequential capsule manufacturing from free base and L-malate salt API's. As we discussed that the equipment will be dry cleaned (removing excipients from the equipment) after completing one batch and before moving to the next batch with different excipient. What we agreed was to get some scientific rationale from you and Peter to assure that the amount of free base traces left in the equipment will be non-detectable. Peter is preparing a summary of genealogy of SU010398 lot (A)5975-MTM-002 to justify that impurities in SU010398 are similar or lower than those in SU011248 lot. I will appreciate if we get some scientific rationale from you regarding this what you had agreed to provide us.

I am sorry that I did not get back to you earlier because the manufacturing plan was changed when I returned (Capsule manufacturing from the free base API only) but now it has been changed back to the same what we had discussed

With Best Regards

Sardar Ali
QA Product Release Manager
SUGEN, Inc.
230 East Grand Avenue
South San Francisco
Phone: (650) 837-3648
Fax: (650) 837-3326

LOT I83K01 [initials] *29 MAY 2002*
ATTACHMENT 5

PHARMACEUTICAL DEVELOPMENT

FINISHED PRODUCT AND PACKAGING MATERIAL REQUEST

PRODUCT:	PHARMACEUTICAL FORM:
SU10398	*GRANULATE*
Dosage: *75% P/P*	Lot: I83K01
Approved: O	Under analysis: Ø

Quantity requested: *L280* units equal to / g (Average unit weight:)

Quantity sent: *4280** units

Product: loose *x* packaged

Purpose of the request: stability packaging

other: *Preparation lot I83G02*

PACKAGING MATERIAL					
MATERIAL	CODE	LOT	QUANTITY REQUESTED	QUANTITY SENT	UNDER ANALYSIS

REQUESTING SECTION: *Oral Solids*	PRODUCT PREPARATION	PRODUCT COLLECTION
Date: *11/02/01* Signature: [signature]	Date: *12-04-01* Operator's signature: [signature] Verifier's signature: [signature] Chief's signature: [signature]	Date: *12-6-01* Signature: [signature]

QUALITY ASSURANCE APPROVAL OR DELEGATION FOR THE COLLECTION OF THE PRODUCT STILL UNDER ANALYSIS

Date: *12/4/2001*
Signature: [signature]

MTH014_4

**Delivered all of it to stock*
[signature] *12 April 2001*

LOT I83G02

PHARMACEUTICAL DEVELOPMENT
EXCIPIENTS REQUEST

PRODUCT: *SU 10398*				
LOT/PREPARATION: *I83G02*				
PHARMACEUTICAL FORM: *CPS*			DOSAGE: *50 mg (AS FREE BASE)*	
SCOPE OF THE PREPARATION: *CLINICAL SUPPLY*				
EXCIPIENT NAME	CODE	LOT	QUANTITY (in grams)	UNDER ANALYSES
F3 T/C SWEDISH ORANGE GEL CAPSULES	*1491*	*AE283*	*CIRCA 65000 CPS*	*
			= $p_0$2.3185	
		[initials] *03/04/01*		
NOTES: *MAKE READY BEFORE 06 APRIL 2001* [initials]				

REQUESTING SECTION: *ORAL SOLIDS*	PRODUCT PREPARATION	PRODUCT COLLECTION
Date: *03/04/01*	Date: *04-04-01*	Date: *12-4-01*
Signature: [signature]	Operator's signature: [signature]	Signature: [signature]
	Verifier's signature: [signature]	
	Chief's signature: [signature]	

MTF017_5

WAREHOUSING Section
PRODUCT
F3 T/C SWEDISH ORANGE GEL CPS
LOT

		AE283
Scale		1
Gross		3.447 kg
Tare		0.262 kg
NET		3.185 kg
Date		04.04.01
Time		11.21.15
Operator	[signature]	CANESSA/ANTONINI

PHARMACEUTICAL DEVELOPMENT

PACKAGING MATERIALS REQUEST

PACKAGING MATERIALS					
MATERIAL	CODE	LOT	QUANTITY REQUESTED	QUANTITY SENT	UNDER ANALYSES
KRAFT BARRELS	*771350000*	*VARIOUS*	*N°2*	*2*	
PE BAGS FOR BARRELS	*735573000*	*AA39N054*	*N°10*	*10*	
PE BAGS 350x580mm	*735190000*	*AA38L198*	*N°10*	*10*	
PE BAGS 280x380mm	*735170000*	*AA39D091*	*N°15*	*15*	

PRODUCT TO BE PACKAGED:	PHARMACEUTICAL FORM:
SU10398	*CPS*
Dosage: *50mg (AS FREE BASE)*	Lot: *I83G02.*

REQUESTING SECTION *ORAL SOLIDS*	PRODUCT PREPARATION	PRODUCT COLLECTION
Date: *03/04/01*	Date: *05-04-01*	Date: *11-4-01*
Signature: [signature]	Operator's signature: [signature]	Signature: [signature]
	Verifier's signature:	
	Chief's signature: [signature]	

MTH014_4

NOTE MAKE READY BEFORE 06 APRIL 2001 [initials]

PHARMACEUTICAL DEVELOPMENT

DETERGENTS/DISINFECTANTS REQUEST FOR THE CLEANING OF THE PLANTS

PRODUCT: *SU10398*

LOT/PREPARATION: *I83G02*

DETERGENT/DISINFECTANT NAME	CODE	LOT	QUANTITY	UNDER ANALYSES
PYRONEG	*1453*	*AE259*	*5 Ky*	*

NOTES: _____

REQUESTING SECTION: *ORAL SOLIDS*	PRODUCT PREPARATION	PRODUCT COLLECTION
Date: *03/04/01*	Date: *04-04-01*	Date: *22-4-01*
Signature: [signature]	Operator's signature: [signature]	Signature: [signature]
	Verifier's signature: [signature]	
	Chief's signature: [signature]	

MTF017_5

[signature]

WAREHOUSING Section

PRODUCT

PYRONEG

LOT

AE259

Scale	1
Gross	5.263 kg
Tare	0.263 kg
NET	5.000 kg
Date	04.04.01
Time	12.35.41
Operator [signature]	CANESSA/ANTONINI

LOT I83G02
ATTACHMENT 8 [initials] *27 MAY 2001*

Pharmacia & Upjohn

PILOT PLANT FORMULATION DEVELOPMENT

FINISHED PRODUCT DELIVERY FORM

DATE: *10* / *MAY* / *01*

PRODUCT: *SU10398* PREPARATION DATE: *04* / *01* APPROVED

LOT: *I83G02* UNDER ANALYSES *X*

DOSAGE: *50 mg* FORMULA NO.: *83HCO1*

RAW MATERIAL LOT: *(A) 5975-MTM-0002-M2 (97.93%)*

QUANTITY *41875* + COUNTER SAMPLE *100* TOTAL *41975*

ADMINISTRATION: oral ☒ injectable ☐ topical ☐ drops ☐

PHARMACEUTICAL FORM

LYOPHILE ampoule ☐ vial ☐

SOLUTION/SUSPENSION bottle ☐ vial ☐ ampoule ☐ small flask ☐ bag ☐

OINTMENT tube ☐ jar ☐

gel ☐ cream ☐ paste ☐ salve ☐

TABLET simple ☐ film-coated ☐ sugar-coated ☐

gastrointestinal ☐ soluble/effervescent ☐

dimensions/form:

average weight:

packaging:

CAPSULE hard gelatin ☒ soft gelatin ☐ *136.1* [initials] *10/5/01*

format: *3* average weight: ~~*136.26 µg*~~

color: *T/C OPAQUE SWEDISH ORANGE*

printing:

packaging: *1 BARREL*

POWDER/GRANULATE oral ☐ injectable ☐ inhalational ☐

packaging:

STORAGE room temperature ☒ +1°C ☐ -20°C ☐ -80°C ☐

other conditions:

POSSIBLE NOTES:

PERSON IN CHARGE: [signature]

Pharmacia & Upjohn
Pharmaceutical Development

Analyses Report

Laboratory Information Management System

Submission Id: 113751
Sample ID (Request No.):20011710
User sample ID (lot):**163G02**
Sample Type: SU010398 (PNU290940AD) CAPSULE 50 MG

Stability Study: I83G02
Pack Type: BULK
Storage Condition: TIME ZERO
Time Label: TIME ZERO
Preparation purpose: STABILITY

Condition : APPROVED
Status : COMPLETE

Samples Notes:

Method	Controls	Results	M.U.	Spec?	Lower lim	Upper lim	Book–Data Analyses	Analyst	Verifier
083GCO01#01	APPEARANCE	COMPLIANT	txt				75/35 - JUN 2001	PASTO	MARIANI
083GIZ01#01	HPLC IDENTIFICATION	POSITIVE	txt				75/35 - JUN 2001	PASTO	MARIANI
083GTI01#01_R	(HPLC TITER)SAMPLE#1	98.3	%		95.000	- 105.000	75/35 - JUN 2001	PASTO	MARIANI
	(HPLC TITER) SAMPLE#2	97.7	%		95.000	- 105.000	75/35 - JUN 2001	PASTO	MARIANI
	(HPLC TITER) SAMPLE#3	98.1	%		95.000	- 105.000	75/35 - JUN 2001	PASTO	MARIANI
	AVERAGE TITER (HPLC)	98.03	%		95.000	- 105.000	75/35 - JUN 2001	PASTO	MARIANI
083GSC01#00	TOTAL CORRELATED SUBSTANCES	1.3	%				75/35 - JUN 2001	PASTO	MARIANI
	IMPURITIES NOT LESS THAN 0.05%	SEE TEXT	%				75/35 - JUN 2001	PASTO	MARIANI
083GKF01#00	(HUMIDITY) SAMPLE #1	1.48	%				75/35 - JUN 2001	PASTO	MARIANI
	(HUMIDITY) SAMPLE #2	1.63	%				75/35 - JUN 2001	PASTO	MARIANI
	(HUMIDITY) SAMPLE #3	1.67	%				75/35 - JUN 2001	PASTO	MARIANI
	AVERAGE HUMIDITY	1.59	%				75/35 - JUN 2001	PASTO	MARIANI

Pharmacia & Upjohn
Pharmaceutical Development

Analyses Report

Laboratory Information Management System

Submission Id: 113751
Sample ID (Request No.): 20011710
User sample ID (lot): I83G02
Sample Type: SU010396 (PNU290840AD) CAPSULE 50 MG

Stability Study: I83G02
Pack Type: BULK
Storage Condition: TIME ZERO
Time Label: TIME ZERO
Preparation purpose: STABILITY

Condition:
APPROVED
Status:
COMPLETE

Samples Notes:

Method	Controls	Results	M.U.	Spec?	Lower lim	Upper lim	Book-Data Analyses	Analyst	Verifier
083GUP01#01	SAMPLE#1	97.4	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#2	101.2	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#3	101.3	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#4	100.3	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#5	102.2	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#6	98.2	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#7	96.4	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#8	97.2	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#9	95.5	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#10	105.6	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#11	97.3	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#12	97.3	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#13	98.2	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#14	103.7	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#15	99.2	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#16	95.7	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#17	95.8	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#18	99.8	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#19	96.3	%		85.000	115.000	75/35 - JUN 2001	PASTO	MARIANI

Submission Id: 113751
Sample ID (Request No.): 20011710
User sample ID (lot): I83G02
Sample Type: SU010398 (PNU290940AD) CAPSULE 50 MG
Samples Notes:

Stability Study: I83G02
Pack Type: BULK
Storage Condition: TIME ZERO
Time Label: TIME ZERO
Preparation purpose: STABILITY

Condition:
APPROVED
Status:
COMPLETE

Method	Controls	Results	M.U.	Spec?	Lower lim	Upper lim	Book-Data Analyses	Analyst	Verifier
083GUP01#01	SAMPLE#20	97.5	%		85.000	- 115.000	75/35 - JUN 2001	PASTO	MARIANI
	AVERAGE WEIGHT	98.61	%		85.000	- 115.000	75/35 - JUN 2001	PASTO	MARIANI
	STANDARD DEVIATION	2.922	std-1				75/35 - JUN 2001	PASTO	MARIANI
	C.V.	2.96	%				75/35 - JUN 2001	PASTO	MARIANI
	MIN. DISSOLUTION VALUE	95.5	%		85.000	- 115.000	75/35 - JUN 2001	PASTO	MARIANI
	MAX. DISSOLUTION VALUE	105.6	%		85.000	- 115.000	75/35 - JUN 2001	PASTO	MARIANI
083GDS01#01_12									
083GMC01#01	TOTAL AEROBIC BACTERIA	IN LIMITS	bd				BIOLAB MAY 2001	PASTO	MARIANI
	ESCHERICHIA COLI	ABSENT	bd				BIOLAB MAY 2001	PASTO	MARIANI
	SALMONELLA	ABSENT	bd				BIOLAB MAY 2001	PASTO	MARIANI
	FUNGI	IN LIMITS	bd				BIOLAB MAY 2001	PASTO	MARIANI
	STAPHYLOCOCCUS AUREUS	ABSENT	bd				BIOLAB MAY 2001	PASTO	MARIANI
	ENTEROBACTERIA	ABSENT	bd				BIOLAB MAY 2001	PASTO	MARIANI

Submission Id: 113751
Sample ID (Request No.): 20011710
User sample ID (lot): I83G02
Sample Type: SU010398 (PNU290940AD) CAPSULE 50 MG

Stability Study: I83G02
Pack Type: BULK
Storage Condition: TIME ZERO
Time Label: TIME ZERO
Preparation purpose: STABILITY

Condition:
APPROVED
Status:
COMPLETE

Samples Notes:

Method	Controls	Results	M.U.	Spec?	Lower lim	Upper lim	Book-Data Analyses	Analyst	Verifier
083GDS01#01_12	SAMPLE#1	97.5	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#2	100.5	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#3	99.0	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#4	95.5	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#5	99.9	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#6	97.2	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#7	98.7	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#8	99.3	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#9	97.6	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#10	98.7	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#11	99.0	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	SAMPLE#12	99.0	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	DISSOLUTION	98.51	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	STANDARD DEVIATION	1.335	std-1				75/35 - JUN 2001	PASTO	MARIANI
	C.V.	1.36	%				75/35 - JUN 2001	PASTO	MARIANI
	MIN. DISSOLUTION VALUE	95.5	%		80.000		75/35 - JUN 2001	PASTO	MARIANI
	MAX. DISSOLUTION VALUE	100.5	%		80.000		75/35 - JUN 2001	PASTO	MARIANI

Submission Id: 113751
Sample ID (Request No.): 20011710
User sample ID (lot): **I83G02**
Sample Type: SU010398 (PNU290940AD) CAPSULE 50 MG

Stability Study: I83G02
Pack Type: BULK
Storage Condition: TIME ZERO
Time Label: TIME ZERO
Preparation purpose: STABILITY

Condition :
APPROVED
Status :
COMPLETE

Samples Notes:

Observations on the Method 083GCO01#00, component: APPEARANCE
Opaque brick red colored shaped hard gelatin capsule containing yellow-orange colored powder

Observations on the Method 083GDS01#01_12, component: MAXIMUM DISSOLUTION VALUE
no comment

Observations on the Method 083GDS01#01_12, component: DISSOLUTION
Average dissolution at 15 minutes: 97.7% (C.V. 2.6%)
Average dissolution at 30 minutes: 96.5% (C.V. 1.4%)
Average dissolution at 45 minutes: 99.5% (C.V. 1.7%)

Observations on the Method 083GMC01#01, component: TOTAL AEROBIC BACTERIA
Total bacteria count < 10 Ufc/g (Report No. 01.1231)

Observations on the Method 083GMC01#01, component: ENTEROBACTERIA
Enterobacteria < 10 Ufc/g (Report No. 01.1231)

Observations on the Method 083GMC01#01, component: ESCHERICHIA COLI
Test done on 10g (Report No. 01.1231)

Observations on the Method 083GMC01#01, component: FUNGI
Fungi (yeasts and molds) < 10 Ufc/g (Report No. 01.1231)

Observations on the Method 083GMC01#01, component: SALMONELLA
Test done on 10g (Report No. 01.1231)

Observations on the Method 083GMC01#01, component: STAPHYLOCOCCUS AUREUS
Report No. 01.1231

Observations on the Method 083GSC01#00, component: IMPURITIES NOT LESS THAN 0,05%

Submission Id: 113751
Sample ID (Request No.): 20011710
User sample ID (lot): **I83G02**
Sample Type: SU010398 (PNU290940AD) CAPSULE 50 MG

Stability Study: I83G02
Pack Type: BULK
Storage Condition: TIME ZERO
Time Label: TIME ZERO
Preparation purpose: STABILITY

Condition :
APPROVED
Status :
COMPLETE

Samples Notes:

Observations on the Method 083GSC01#00, component: IMPURITIES NOT LESS THAN 0.05%

RRT 0.690 (Impurities A) : 0.16%
RRT 0.913 (Impurities B) : 0.09%
RRT 0.926 (Impurities C) : 0.15%
RRT 1.069 (Impurities D) : 0.28%
RRT 1.089 (Impurities E) : 0.11%
RRT 1.142 (Impurities F) : 0.07%
RRT 1.261 (Impurities G) : 0.13%
RRT 1.272 (Impurities H) : 0.15%
RRT 1.646 (Impurities I) : 0.16%

Observations on the Method 083GUP01#00, component: AVERAGE WEIGHT
The average weight of 98.51% corresponds to 87.65 mg/capsule

Approved by: MARIANI
Approval date: 13-jun-2001

PRODUCT/MATERIAL:
SU010398 50mg CAPSULE

NUMBER(S) OF THE LOT(S)/PACKAGING RUN:
I83K01 and I 83G02

DATE (AND TIME WHERE POSSIBLE) OF THE DEVIATION:
15 June 2001

DESCRIPTION OF PROPOSED DEVIATION:

1 - Absence of the following instructions on the Processing Sheet regarding what is described in the product's Process Flow Chart: start time and end time registration of lot I82K01, Granulation operations (start time Num. 3) and Num. 13 and on the I82G02 sheet, operations Num. 2 and Num. 12.
2 - Encapsulation operations during the period from the 12th to the 24th of April

SIGNATURE/DATE: [signature] *June 15th, 2001*

REASON FOR THE DEVIATION AND INVESTIGATION:

1 - lack of registration indications in the filling in the Processing Sheet by Oral Solids
2 - The extended period is due to the Easter Holidays and unexpected technical difficulties, namely the adhesion of the mix to the walls of the hopper. Stability data for the month regarding a technical capsule lot (1985-013) support the granulate's stability for a period of 12 days, which is the duration of the capsule preparation process.

[signature] *15/6/01* SIGNATURE/DATE: [signature] *June 15th, 2001*

IMMEDIATE CORRECTIVE ACTIONS:
NONE

SIGNATURE/DATE:

SECTION CHIEF:

QA/QUALITY SYSTEMS:

1 - Oral Solids will perform the filling out of the Process Sheet in accordance with the Process Flow Chart prior to the next productions
2 - If in future production the time is prolongated longer than expected, appropriate analytic controls will be performed on the granulate to verify the product's stability. For this purpose a portion of granulate must be collected at the beginning of encapsulation, which is to be kept at +2° - ÷8° C, in case an initial reference sample is needed.

[signature] *June 15th, 2001*

SECTION CHIEF:

[signature]

QA/QUALITY SYSTEMS:

[signature] *18/06/01*

COMPLAINT N° 24 / 2002

Product: SU011248 L-malate 50 mg capsules - Lot I83G02 (manufacturing date April 2001)

REASON FOR THE COMPLAINT:

EVIDENCED IN A CLINICAL CENTER A CAPSULE WITH CRUSHED END CONTAINED IN ONE BOTTLE OF THE DRUG (COMMUNICATION FROM SUGEN - see enclosure 1)

ENCHARGED PERSON OF THE INVOLVED SECTION	DATE OF RECEIPT OF THE COMPLAINT
ALESSANDRA CAVALLO	• ORAL SOLIDS R&D: **21.11.2002** • QA: **21.11.2002**

DETAILED DESCRIPTION OF THE DEFECT:

PRIMARY DEFECT: CAPSULE WITH CRUSHED END

INVESTIGATION RESULTS:

THE 3% OF THE LOT WAS INITIALLY INSPECTED (1260 CPS ON 41985), FINDING OUT 7 UNITS WITH BROKEN END. AS THE ACCEPTANCE LIMIT IS OF THREE UNITS, THE LOT WAS 100% VISUALLY INSPECTED (MANUAL OPERATION) ACCORDING TO SOP SF.TF 025, DISCHARGING ALL THE DEFECTIVE CAPSULES (6 UNITS FOR BROKEN END, 3 UNITS FOR BROKEN BODY, 3 UNITS FOR VISUALIZATION OF THE BODY ON THE TOP AND 378 UNITS FOR CRUSHED ENDS)

THE ROOT CAUSE OF THE EVIDENCED DEFECTS IS ATTRIBUTABLE TO THE NOT CORRECT REGULATION OF THE PUNCHES CLOSING THE CAPSULES

IMMEDIATE CORRECTIVE ACTIONS (indicate who is responsible for / completion date):

NO IMMEDIATE ACTION - THE EVIDENCED DEFECT DO NOT HAVE ANY IMPACT ON THE PRODUCT EFFICACY OR SAFETY FOR THE PATIENT

SIGNATURE/DATE: Laura Facchetti 18/12/2002

MEAN/LONG TERM CORRECTIVE ACTIONS (indicate who is responsible for / completion date):

- **THE PUNCHES CLOSING THE CAPSULES ARE SET UP BEFORE EACH PRODUCTION, TRYING TO OPTIMIZE THE REGULATION. PARTICULAR ATTENTION WILL BE DEVOTED TO THIS ASPECT AS FOR FURTHER ENCAPSULATION PROCESSES.**
  (Alessandra Cavallo Responsible for).
- **A TRAINING SESSION FOR THE OPERATORS PERFORMING VISUAL INSPECTIONS WILL BE ORGANIZED**
  (Alessandra Cavallo Responsible for; foreseen completion date: end February, 2003).

CONCLUSIONS:

THE EVIDENCED DEFECT IS ATTRIBUTABLE TO OPERATOR'S OVERLOOKING. NO COMPLAINT AS FOR THE SAME DEFECT HAS UNTIL NOW BEEN RECEIVED.

SIGNATURE/DATE: Laura Facchetti

18/12/2002

[redacted]

REASON FOR THE COMPLAINT:

A CLINIC REPORTED THE PRESENCE OF A CAPSULE WITH A CRUSHED BASE IN A PACKAGE OF THE DRUG (SUGEN COMMUNICATION- ATTACHMENT 1)

ENCHARGED PERSON OF THE INVOLVED SECTION	CLAIM RECEIVED ON AND BY:
ALESSANDRA CAVALO	• 21 November 2002 by ORAL SOLIDS R&D • 21 November 2002 by QA

DETAILED DESCRIPTION OF THE DEFECT:

PRIMARY DEFECT – CAPSULE BASE CRUSHED –

INVESTIGATION RESULTS:

3% OF THE LOT WAS INITIALLY INSPECTED (1260 CAPSULES OUT OF 41985) WITH THE DETECTION OF 7 DEFECTIVE UNITS DUE TO RUPTURE AT THE TIP. SINCE THE LIMIT OF THREE DEFECTIVE UNITS WAS EXCEEDED, THE LOT WAS SORTED BY UNIT (MANUAL OPERATION), ACCORDING TO THE PROCEDURE SF.TF 025, IN ORDER TO ELIMINATE ALL DEFECTIVE CAPSULES (6 UNITS FOR TIP RUPTURE AT THE TIPS, 3 UNITS FOR FRACTURE OF THE CAPSULE BODY, 3 UNITS FOR THE VISUALIZATION OF THE BODY ON THE TOP, AND 378 UNITS FOR CRUSHED TIPS).
THE CAUSE OF THE DEFECTS FOUND CAN BE ATTRIBUTED TO THE INCORRECT REGULATION OF THE PUSHING ELEMENTS FOR CLOSING THE CAPSULES.

IMMEDIATE CORRECTIVE ACTIONS (indicate who is responsible for / completion date):

NONE- The nature of the discovered defects did not have any impact on patient safety and/or the drugs efficacy.

SIGNATURE/DATE: [signature] *18/12/2002*

MEAN/LONG TERM CORRECTIVE ACTIONS (indicate who is responsible for / completion date):

- THE PUSHING ELEMENTS TO CLOSE THE CAPSULES ARE MOUNTED PRIOR TO EACH ENCAPSULATION, IN AN ATTEMPT TO ACHIEVE THE OPTIMAL REGULATION. PARTICULAR ATTENTION WILL BE GIVEN AT THE START OF FUTURE PROCESSING.
(Person in Charge Alessandra Cavallo).

- TRAINING SESSIONS WILL BE ARRANGED FOR THE OPERATORS OF THE SORTING OPERATIONS
(Person in Charge Alessandra Cavallo; date planned for completion: End of February 2003).

CONCLUSIONS:

THE DETECTED DEFECT IS ATTRIBUTED TO THE OPERATOR'S MISTAKE DURING THE SORTING PHASE. AS YET NO CLAIM OF ANY KIND HAS BEEN RECEIVED.

SIGNATURE/DATE: [signature]
18/12/2002